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Triazolam and Temazepam: Issues and Concerns Relevant to the Army Aviation Community

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The use of hypnotics in Army aviation has become an option for helping soldiers sleep in less than optimal environments and in unusual circumstances, e.g., preparing for deployment to another time zone, or during high intensity combat. The choice of a hypnotic for aviator use is limited since a grounding period is needed while the medication is effective and performance may be compromised for several hours postadministration. The two hypnotics currently used by the aviation community are temazepam (Restoril®) during peace time and triazolam (Halcion®) during war time. The present paper briefly reviews laboratory and clinical studies of these two hypnotics. In addition, the advantages and disadvantages of each medication are discussed as well as the current Army policy concerning the use of such medications. Recommendations concerning studies needed to assess the effects of these medications on pilot performance are provided.

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Military relevance

In many instances associated with training exercises and combat situations, Army personnel are required to adhere to arduous work schedules which often result in the disruption of sleep, high stress levels, and fatigue. Such instances include the rapid deployment of Army personnel across meridians, the rapid transition from daytime to nighttime duty hours, and the extension of duty hours in order to accomplish mission objectives.

Often, it is difficult for military personnel to obtain enough sleep, particularly when the timing of rest periods becomes unpredictable. Rapidly crossing meridians or sudden changes in sleep schedules (e.g., night operations) can result in insomnia, disturbed mood, cognitive degradation, and reduced alertness (Comperatore and Krueger, 1990). In order to prevent sleep loss and its consequences during military deployments and night operations, the Army research and medical community has been exploring countermeasures. One alternative consists of the use of short-acting benzodiazepines, a family of drugs known to facilitate sleep, both in terms of onset time and duration. Because of the side effects associated with benzodiazepine use, the regulation of their administration to Army aviation personnel requires precise knowledge of their impact on performance within the operational context.

Background

Since Army aviation developed the necessary technology to sustain operations around the clock, aviators often are required to transition from daytime to nighttime duty within 24 hours, without the benefit of an adaptation period. Often, the work schedules used in night operations require the sleep period to occur, partially and sometimes entirely, during daylight hours. In these circumstances, physiological adjustment to the new work/rest schedule is difficult, particularly when sleeping quarters are located in a field setting. Environmental factors such as noise and temperature may disrupt sleep and delay the normal process of adaptation to the new work/rest schedule. Similar problems are associated with rapid (within 24 hours) troop deployment across time zones.

In order to alleviate some of the problems associated with both nighttime work and transmeridian deployment, the Army aviation community has developed guidelines to assist in the adaptation to the new schedule. One proposal has been to use a hypnotic to promote sleep during the normal physiological process of adaptation to the new work/rest schedule. Two medications recommended by the aviation medical community are temazepam (Restoril®) and triazolam (Halcion®).

An extensive literature review has revealed that research on the properties and effects of benzodiazepines includes the fields of cognition, psychomotor performance, sleep architecture, pharmacology, circadian rhythms, neurology, and psychiatry. However, studies focusing on the impact of benzodiazepine use on human performance within the aviation environment are few. The objective of this report is to review the issues, concerns, advantages, and disadvantages associated with the current use of temazepam and triazolam in the context of Army aviation.

Temazepam

Pharmacokinetics. Temazepam (3-hydroxydiazepam) is considered an intermediate acting hypnotic with a half-life of approximately 10 hours in the formulation marketed in the U.S. (hard gelatin capsule). Its only known active metabolite is oxazepam (Breimer, 1979; McElnay, Jones, and Alexander, 1982; Nicholson and Stone, 1987). The formulation marketed in Europe, a soft gelatin capsule, exhibits a shorter half-life of approximately 5 to 8 hours (Fucella et al., 1977). The mean delay to peak plasma concentration is approximately 1 hour for the soft gelatin formulation. However, the formulation marketed in the U.S. (hard gelatin capsule) increases the time of absorption and the mean delay to peak plasma concentration (2.2 hours). In general, the intermediate elimination half-life of temazepam and lack of active metabolites makes its use desirable in aviation since pilots need not be grounded for more than 12 hours post-administration. Other hypnotics such as barbiturates or over-the-counter sleeping aids require grounding periods of 72 hours and 24 hours respectively (Department of the Army, 1989).

Effects on sleep. Temazepam can be used for both induction and maintenance of sleep, but its application and dose depend on the formulation. The soft gelatin capsule marketed in Europe has a characteristic brief absorption rate. In this case, a low dose (10 to 20 mg) of temazepam is effective in the reduction of time to sleep onset. On the other hand, the hard gelatin capsule formulation marketed in the U.S. has a longer absorption rate and is less efficient in the rapid induction of sleep (Nicholson and Stone, 1986, 1987). This formulation tends to promote the use of larger doses of temazepam, thus exacerbating associated side effects. Small dosages of 15 mg of the hard capsule temazepam formulation have not been shown to consistently improve sleep onset time, probably due to the slow absorption rate of the capsule (Kales et al., 1986; Mitler et al., 1979; Roth et al., 1979). Thus, the recommended clinical dosage of the hard capsule formulation temazepam currently is 30 mg.

In general, the effect of temazepam (30 mg) on sleep consists of improved sleep maintenance by reducing the number of

awakenings during the night. No reduction in sleep onset has been documented consistently using the formulation available in the United States. Temazepam has not been reported to disturb significantly the normal architecture of sleep.

Effects on circadian rhythms. As is the case with other tranquilizer and hypnotic drugs (e.g., triazolam and loflazepate), temazepam has not been shown to reentrain physiological rhythms such as those of body core temperature, 6-sulphatoxymelatonin, and cortisol (Donaldson and Kennaway, 1991; Smolensky and Reinberg, 1990). Consequently, its value in terms of amelioration of desynchronosis symptomatology resides in the maintenance of sleep and the reduction of fatigue (Donaldson and Kennaway, 1991).

Side effects. In general, the reports of severe side effects involving the use of temazepam are low (Regestein and Reich, 1985; Rickels, 1983). Single doses of temazepam (30 mg) were shown consistently to increase drowsiness and induce sleep within 2 hours postadministration, while doses of 5 and 15 mg had no discernible effects (Matejcek et al., 1983). Some studies have shown impairment in both cognitive and motor performance during morning tests after 30 mg nighttime administration of temazepam (Nicholson, 1979; Roth et al., 1985). However, other studies have not shown morning performance decrements after 30 mg or less of temazepam (Hindmarch, 1979; Roehrs et al., 1986). Anger and agitation also have been reported by insomnia patients treated with daily doses of temazepam (30 mg) for short periods (1 to 6 days) (Regestein and Reich, 1985). In a controlled study using 55 outpatients with insomnia, reported side effects of hangover, dizziness, nightmares, and constipation occurred with approximately the same frequency in both temazepam (30 mg) and placebo. However, severe side effects, including depression, lethargy, headache, irritability, and restlessness, were reported eight times in the temazepam group and five times in the placebo group (Heffron and Roth, 1979). In a 3-month study of temazepam (30 mg) and midazolam (15 mg) involving 175 patients with chronic insomnia, 24.2 percent of patients receiving temazepam reported side effects. The most frequently reported effects were somnolence (N=5), headaches (N=7), dizziness (N=4), and amnesia (N=3). These effects did not differ significantly from the reports given by the midazolam group. One patient experienced a severe headache and severe depression after taking temazepam for 6 nights, after which he was removed from the study (Allen et al., 1987).

Tolerance. The issue of drug tolerance has been addressed by several researchers. Studies have indicated both rapid tolerance to temazepam (Kales et al., 1986) as well as no tolerance for 5 to 7 weeks (Allen et al., 1987; Mitler et al., 1979). The reason for such discrepancy may be in the dosages

used in these studies-- Kales and associates used 15 mg of temazepam while the other studies used 30 mg dosages.

Use in Army aviation. The use of temazepam (30 mg) by aircrew is recommended for predeployment rest only and requires a temporary grounding period of 12 hours postadministration. Regulations require an initial evaluation of aircrews upon introduction to the medication to ensure the aircrewmember is free of significant side effects (Department of the Army, 1989). During Operation Desert Storm, temazepam was the second choice of sleep medications. An initial test dose to determine adverse reactions to the medication was required, followed by a grounding period of 24 hours. After passing the test dose, temazepam (30 mg) could be administered once a day for no more than 7 consecutive days, with a grounding period of 8 hours post-administration. Reasons for administering temazepam were to aid in adjustment to sleep outside one's normal sleep period, or to aid sleep during high intensity combat flight operations (Department of the Army, 1991). During both peacetime and wartime, temazepam can be used only under the supervision of a flight surgeon.

Triazolam

Pharmacokinetics. Triazolam is a benzodiazepine derivative which exhibits a short parent drug half-life of approximately 5 hours. A major metabolite, alpha-hydroxytriazolam, also is rapidly eliminated. The pharmacokinetic properties of triazolam have been shown to vary with the time of administration. Triazolam (0.5 mg) administered at 2000 hours resulted in significantly greater elimination times (half-life = 3.77 hours) than administrations at 0700 hours (half-life = 2.94 hours), while absorption rate was faster during daytime (mean = 13.3 minutes; standard error = 6.9) than during evening hours (mean = 21.9 minutes; standard error = 15.6). For review, see Reinberg, Smolensky, and Labrecque (1987).

Effects on sleep. The recommended clinical dose of triazolam is 0.25 mg (0.125 mg for the elderly). Studies using both 0.25 mg and 0.5 mg dosages have shown improvement in sleep onset and sleep maintenance, with fewer number of awakenings after sleep onset (Goetzke, Findeisen, and Welbers, 1983; Johnson et al., 1987; Ogura et al., 1980; Vogel et al., 1975). The effects on sleep architecture after short-term (up to 14 days) use are increases in stage 2 sleep (.25 and 0.5 mg), increases in the latency of the first rapid eye movement (REM) period (0.5 mg only), but no decrease in total percent REM for the night, and no significant decrease in slow wave sleep (Kubicki et al., 1987; Roth, Kramer, and Lutz, 1976). In contrast, intermediate-term administration (up to 18 days) of 0.5 mg of triazolam has been shown to result in more changes in sleep architecture. Kales and

coworkers (1976) reported significant reductions of percent time of REM sleep and stage 3 sleep, and corresponding increments in percent time of stage 2 sleep.

Effects on circadian rhythms. Triazolam (0.5 and 0.25 mg) has been shown to improve daytime sleep, with reduced sleep onset time, decreased number of awakenings after sleep onset, and increased total sleep time when compared to daytime sleep without a sleeping aid (Balkin et al., 1988; Nicholson, Stone, and Pascoe, 1980; Walsh et al., 1988; Walsh, Muehlbach, and Schweitzer, 1984). Although sleep was improved during the day, triazolam (0.5 and 0.25 mg) did not improve the ability of night workers to adapt to the new schedule, nor was performance and alertness improved during the normal circadian drop in these measures (Balkin et al., 1989; Walsh, Muehlback, and Schweitzer, 1984; Walsh et al., 1988). One study by Walsh and associates (1984) did note an improvement in subjective alertness when shift workers were administered triazolam (0.5 mg) during the day. They attributed this effect to a decrease in sleep deprivation which normally occurs in daytime sleep. Triazolam has been shown to improve sleep in terms of sleep onset and duration, but has not been shown to resynchronize circadian rhythms (Office of Technology Assessment, 1991; Rosa et al., 1990). Triazolam also has been recommended for use in the amelioration of jet-lag symptoms related to transmeridian translocations (Reinberg, Smolensky, and Labrecque, 1987).

Side effects. Although one desirable characteristic of triazolam is its short half-life (2 to 5 hours), there is controversy associated with the use of triazolam due to adverse side effects reported in the literature (Nicholson and Stone, 1987). Initial evaluation of triazolam indicated reports of side effects ranging from 10 percent for hangover to less than 5 percent for headache, dizziness, dry mouth, and nervousness in patients receiving 0.25 or 0.5 mg. Earlier reports from investigators studying dosages of 1.0 mg reported hangover effects approximately three times greater than those reported with 0.5 mg dosages (Kroboth and Juhl, 1983).

Several studies investigating 0.25 and 0.5 mg dosages of triazolam report side effects which include anxiety, restlessness, impaired performance on the following day, and sedation (Borbely et al., 1983; Cohn, 1984; Costa e Silva et al., 1983; Gorenstein and Gentil, 1983; Leibowitz and Sunshine, 1978; Morgan and Oswald, 1982). Performance decrements have been documented up to 6.5 hours postdose, with baseline levels being reached in 8 to 10 hours postdose (Balkin et al., 1988; Bornstein, Watson, and Kaplan, 1985; Ogura et al., 1980; Roache and Griffiths, 1985; Spinweber and Johnson, 1982). These decrements usually are seen after 0.5 mg of triazolam, with few decrements in performance reported after the 0.25 mg dose.

Borbely and associates (1983) found performance decrements on a psychomotor test after administering the 0.5 mg dose of triazolam, but did not find a significant decrement after the 0.25 mg dose. Gorenstein and Gentil (1983) found sedation and performance effects up to 10 hours postdose with 0.5 mg triazolam, but only up to 6 hours postdose with 0.25 mg. Johnson and associates (1987) investigated the arousal threshold of 36 insomniac patients taking either 0.25 mg or 0.5 mg triazolam for 5 nights. Both doses of triazolam significantly increased the reaction time to a smoke detector alarm on the first night, with 16 subjects failing to awaken at all and the slowest arousal seen with 0.5 mg. However, some tolerance was seen by night 4, with only 12 subjects failing to respond to the alarm. Most of these subjects who failed to awaken to the alarm were in slow wave sleep, but some subjects also failed to respond when the alarm was sounded during stage 1 or stage 2 sleep.

Another potential side effect reported in the literature is rebound insomnia, a reduction in total sleep after discontinuation of medication compared to baseline mean values. This effect has been reported in association with triazolam (0.5 mg) use of at least 3 consecutive weeks (Adam, Oswald, and Shapiro, 1984; Kales et al., 1976; Kales et al., 1979; Leibowitz and Sunshine, 1978; Monti, 1981; Morgan, Adam, and Oswald, 1984). Other studies using either 0.25 or 0.5 mg triazolam for shorter periods (7 nights or less) have not shown evidence of rebound insomnia (Borbely et al., 1983; Spinweber and Johnson, 1982).

The most serious side effects have been anterograde amnesia and mood changes. Several researchers have found that subjects taking 0.5 mg triazolam have difficulty recalling significant events which occurred during the night or performed poorly on memory tasks given in the morning (Bixler et al., 1991; Roache and Griffiths, 1985; Roth et al., 1980). Increased anxiety also has been documented in patients taking 0.5 mg dosages (Kales et al., 1983; Morgan et al., 1984; Morgan and Oswald, 1982). A letter written by a physician in the Netherlands (van der Kroef, 1979) described side effects of depression, severe anxiety, suicidal ideations, paranoia, hyperacousis, and paresthesias in 25 insomniac patients receiving triazolam. Responses to this letter criticized the report for not stating the dosages of triazolam administered, the interactions with other medications, or the underlying disorders of the patients (Barclay, 1979). Regardless of the criticism, van der Kroef's letter prompted further research into the side effects of triazolam.

In summary, it appears that the side effects associated with triazolam are minimal when the 0.25 mg dosage is used for a short time (less than 3 weeks). However, some patients are still sensitive to triazolam, even at the lower dosage (Greenblatt et al., 1991). Anterograde amnesia may occur with the 0.25 mg

dosage as well. In addition, clinical observations indicate that patients tend to double or triple dosages of a medication prescribed in fractions of a milligram more easily than drugs prescribed in higher milligram dosages, so careful observation of the patients receiving triazolam is required (Rickels, 1983). Finally, the optimal action of triazolam is for a short period, less than 3 weeks, with reduction of the beneficial effects and elevation of the side effects in administrations for longer periods (Gillin, 1991).

Tolerance. Triazolam (0.5 mg) is effective for inducing and maintaining sleep with initial- and short-term drug use. However, insomnia and drug tolerance have been reported in association with long term administration (e.g., 2 to 3 weeks) of triazolam (Adam et al., 1984; Kales et al., 1976; Kales et al., 1983; Monti, 1981). Triazolam (0.25 mg and 0.5 mg) appears to be useful in clinical situations requiring short-term administration (1 to 2 weeks), with no evidence of drug tolerance (Roth et al., 1976; Vogel et al., 1975). For intermediate- and long-term use, its clinical value is questionable due to side effects and tolerance development.

Use in Army aviation. Triazolam currently is not recommended as a sleeping aid during peacetime (Department of the Army, 1989). However, triazolam (0.25 mg) recently was recommended as the first line medication for Army personnel in combat during Operation Desert Storm since its shorter half-life would allow for more operational flexibility. As with temazepam, before prescribing triazolam, an initial test dose was required to determine any adverse reactions to the medication, with a grounding period of 24 hours. Once this test dose was passed, triazolam could be administered once a day, up to 7 consecutive days, with a grounding period of 6 hours postadministration. Recommended uses of this medication were to aid in adjustment to sleep outside one's normal sleep period or to aid sleep during high intensity combat flight operations, and only under the supervision of a flight surgeon (Department of the Army, 1991).

Recommendations

The use of triazolam or temazepam during combat or training situations by Army personnel needs further exploration before a specific policy can be drafted and accepted. Both drugs have relatively short half-lives and are effective in the improvement of sleep quality. However, they may degrade cognitive performance and physiological resources, in some instances even 10 to 12 hours postadministration. The impact of side effects of temazepam and triazolam on performance are expected to be minimal during short-term use and when a considerable time (approximately 10-12 hours) separates the time of drug administration and the onset of the work period. Official recommendations on the use of

triazolam and temazepam require careful consideration of contextual variables such as mission demands, field conditions, available medical supervision, dose response, expected time of administration, circadian changes in pharmacokinetic characteristics, and expected duration of treatment.

In training and combat, emergency situations are likely to occur requiring personnel to awaken from a drug-induced sleep and carry out emergency procedures. Under these circumstances, any drug which increases the time required to awaken or causes memory or psychomotor impairment postadministration will compromise safety. Consequently, in the context of Army aviation, the proper assessment of the utility of either temazepam or triazolam requires, at a minimum, operationally relevant studies characterizing the ability of aviators to awaken from a drug-induced sleep and perform duties safely and efficiently.

Although insufficient data currently are available to make definitive recommendations regarding the use of hypnotics in the Army aviation population, we recognize that flight surgeons are frequently required to make decisions relating to hypnotic use under specific operational settings. The clinical decision of which hypnotic to select should center on considerations of efficacy, potential side effects, and, in certain cases, duration of action. As has been noted, both temazepam and triazolam are effective hypnotics. Triazolam has a significantly shorter half-life than temazepam which may be the overriding consideration under circumstances when it is essential that flight crews not be restricted more than 8 hours. However, there is an increasing body of evidence suggesting that triazolam may induce anterograde amnesia or personality changes in some patients, even at the 0.25 mg dose level. Considering the potentially hazardous results of either of these side effects on aviation personnel, it is advised strongly that patients receiving triazolam be carefully monitored and restricted from flight duties if either side effect is suspected.

The issues presented here are considered to be limited, and not an exhaustive treatment of the possible problems and/or benefits associated with the use of either temazepam or triazolam. More research has been conducted on the effects of triazolam than on the effects of temazepam, leaving comparisons of the two medications inadequate. Currently, the lack of precise information relevant to the issues and concerns presented here limits the effectiveness with which the Army aviation community may use these drugs in the amelioration of fatigue and performance degradation. Future research into the effects of these medications on flight performance is needed, including comparisons of the effects of triazolam and temazepam on flight performance, and assessments of the ability of a pilot to awaken from a drug-induced sleep and perform flight duties. In

addition, an investigation into the ability of the U.S. Army to obtain the European formulation of temazepam may offer a practical alternative to triazolam and temazepam in the hard capsule.

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Appendix A

Pharmacokinectics

	Restoril	Halcion
Half-life:	9.5 - 12.5 h	1.5 - 5 h
Active metabolite	oxazepam	alpha-hydroxytriazolam
Peak plasma concentration	2 - 3 h	1.3 h
Dosage:	30 mg	0.25 mg
Onset of action:	25 - 27 m	15 - 30 m

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